DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 8/17/09 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 5/15/09 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 201,213,220,221,224-226, 237, and 238 are pending in the application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/17/09 has been entered.

It is noted that in applicant's response filed on 7/10/08, applicant elected the following species having the following modification schematic without traverse: a first nucleotide of the sense strand closest to the 5' end of the sense strand having a 2'-O-alkyl modification; a second nucleotide of the sense strand next closest to the 5' end of the sense strand having a 2'-O-alkyl modification; a first nucleotide of the antisense

strand closest to the 5' end of the antisense strand is phosphorylated at its 5' end and the sense strand is devoid of a phosphate at its 5' end; the antisense region includes at least one nucleotide other than first and second antisense nucleotides having a 2' modification; the antisense strand has at least one phosphorothioate internucleotide linkage; a 3' overhang of 1-5 nucleotides on at least one of the sense or antisense strand; and at least one conjugate cholesterol coupled to the 3' end of the sense strand.

Applicant's amendments and/or arguments filed on 8/17/09, with respect to the rejections under 35 USC 112, 1st paragraph (new matter) and 35 USC 103(a) has been fully considered and is persuasive. Therefore, these rejections have been withdrawn.

However, upon further consideration, a new rejection under 35 USC 103(a) is applied as set forth below.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/26/09 has been considered by the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 201, 213, 220, 221, 224-226, 237, and 238 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claim 201 has been amended to require for the siRNA molecule to be "configured" for interacting with a target mRNA. However, this terminology is not supported by the specification and is not defined. Therefore, for purposes of the instant search and corresponding examination, the term is not considered to add any limitation to the claims that is not set forth by the structural requirements of the remainder of the claim.

MPEP §2163.06 notes:

> If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

> Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

A review of the specification does not reveal support for where the claim amendment is found. Should applicant disagree, applicants are encouraged to point out with particularity by page and line number where such support might exist.

There is no support for this claim limitation in the claimed priority documents. Therefore, the effective filing date of the instant claims is considered, for purposes of prior art, to be 10/19/06, which is the filing date of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 201, 213, 220, 221, 224-226, 237, and 238 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giese et al. (US 2004/0180351 A1), in view of Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), Vargeese et al. (US 2004/0110296 A1), Jackson et al. (Nature Biotechnology, 2003, pages 635-637), and Bartelmez et al. (US 6,841,542).

It is noted that the Giese et al. and Vargeese et al. references are cited and of record on the PTO-892 mailed on 9/8/08; and the Elbashir et al. reference is cited and of record on the PTO-892 mailed on 5/15/09. The Jackson et al. reference is of record and cited on the IDS filed on 2/24/09.

The instant claims are directed to a siRNA 18-30 bases in length comprising a sense strand and an antisense strand, wherein the first and second nucleotides closest to the 5' end of the sense strand have a 2'-O-alkyl modification and the remainder of the nucleotides are 2'-OH modified; and an antisense strand that is at least substantially complementary with the mRNA of the target gene and the sense strand. Furthermore, a first nucleotide of the antisense strand closest to the 5' end of the antisense strand is phosphorylated at its 5' end and the sense strand is devoid of a phosphate at its 5' end; the antisense region includes at least one nucleotide other than first and second antisense nucleotides having a 2' modification; the antisense strand has at least one phosphorothioate internucleotide linkage; a 3' overhang of 1-5 nucleotides on at least

one of the sense or antisense strand; and a conjugate, more specifically a cholesterol conjugate.

Giese et al. teach siRNA molecules comprising a sense and an antisense strand, comprising a sense region and an antisense region, respectively, wherein the antisense region is complementary with the mRNA of a target gene and is complementary with the sense region.

Giese et al. teach various combinations and patterns of modifications for siRNA duplexes. Giese et al. teach that the siRNAs can be blunt-ended or can comprise a 3'-overhang of at least one nucleotide on the sense or antisense strand. Giese et al. teach siRNA molecules fully modified with 2'-O-methyl modifications, as well as siRNA modification schematics with alternating 2'-O-methyl regions (see Figure 2, for example). Giese et al. teach an siRNA, for example, that is fully modified with 2'-O-methyl modifications with 2 nt 3'-overhangs on the sense and antisense strands (TT) (see duplex 79A79B in Figure 8, for example).

Giese et al. teach that it is particularly advantageous to inactivate the sense strand of any of the RNAi forms of any of the embodiments, preferably via end modification, and more preferably a 5' end modification. Giese et al. teach that the advantage of this strategy arises from the inactivation of the sense strand which might otherwise interfere with an unrelated single-stranded RNA in the cell (see paragraphs [0103] and [0167]). Furthermore, Giese et al. teach that the 5' end of the antisense strand preferably has a free OH and that the 5' end of the sense strand is modified to inactivate the strand (see paragraph [0103] and Table 1, embodiments 7 and 8).

Giese et al. teach that a 5'-phosphate on the antisense strand is required for siRNA function, suggesting that cells check the authenticity of siRNAs through a free 5' OH which can be phosphorylated and allow only such bona fide siRNAs to direct target RNA destruction (see paragraph [0119]).

Giese et al. teach that each of the design elements may be combined (see paragraphs [0112] and [0113], for example). Giese et al. teach that in addition to the various modifications or designs of the inventive RNAi molecules, further or additional modification of the nucleotides may include the use of a phosphorothioate backbone of the RNAi molecules which may be either complete or partial in order to inhibit endonuclease function (see paragraph [0170]).

Giese et al. teach that 2'-O-alkyl modifications stabilize RNAi molecules against degradation, but to a certain degree this is counterbalanced by the effect that 2'-alkyl modifications generally result in a reduced knockdown activity. Therefore, Giese et al. offers motivation to incorporate 2'-O-alkyl modifications in specific locations, rather than to blanket the siRNA with such modifications. Giese et al. offers motivation to incorporate such modifications in a manner that is minimal enough to not reduce knockdown activity. Giese et al. teach that accordingly, the design of RNAi molecules has to balance stability against activity (see paragraph [0176]). Giese et al. teach that the most efficient molecules were modified at alternating positions of both strands.

Giese teaches incorporation of various 2'-position modifications including amino, fluoro, methoxy, alkoxy, and alkyl (see paragraph [0024]). Giese teaches siRNA molecules wherein each strand comprises a plurality of groups of modified nucleotides

having a modification at the 2'-position whereby each group of modified nucleotides is flanked on one or both sides by a flanking group of nucleotides, wherein the flanking group is either unmodified or is modified with a different modification than the modified groups (see paragraph [0025]).

Giese et al. teach siRNAs with various end modifications on the sense and antisense strand and particularly teach the sense strand should be modified at the 5' end to reduce off-target effects mediated by an otherwise functional sense strand which results in increased specificity of the siRNA which is advantageous for any medical use of the RNAi molecules or any target validation using the siRNA (see paragraphs 0103 and 0173).

Giese et al. does not teach a specific schematic wherein the first two nucleotides of the sense and antisense strands (from the 5' end) are 2'-O-alkyl modified wherein the rest of the nucleotides are 2'-OH and does not teach conjugates.

Elbashir et al. teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. The siRNAs taught by Elbashir et al. mediated RNAi via RISC. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications that retained activity, wherein the modifications were in the 3' terminal regions.

Elbashir et al. teaches that a 5'-phosphate on the target-complementary strand of a siRNA duplex is required for siRNA function (see page 6886, column 2); the siRNA

molecules comprise ribonucleotides (see Fig. 1, for example); duplexes of 21 nt siRNAs with 2 nt 3'-overhangs were the most efficient triggers of sequence-specific mRNA degradation (see abstract, for example); and modification of the overhangs (see page 6881). Elbashir et al. teaches that 2'-deoxy substitutions help to reduce the cost of RNA synthesis and may enhance RNase resistance of siRNA duplexes (see page 6885, column 1).

Vargeese et al. teach conjugates including cholesterol, wherein the cholesterol conjugate is for the delivery of a siRNA molecule (see abstract and paragraph [0009], for example). Vargeese et al. teach that the conjugates are used to facilitate delivery of molecules into a biological system such as a cell. Vargeese et al. teach that the conjugates can impart therapeutic activity by transferring therapeutic compounds across cellular membranes (see paragraph [0009]).

Jackson et al. teach the use of gene expression profiling to characterize the specificity of gene silencing using siRNA and discovered that both the sense and the antisense strand was responsible for off-target gene silencing (see page 636).

Bartelmez et al. discloses solutions to the problem of non-target binding of antisense compounds and teach the antisense strand can be modified to reduce the non-target binding (see column 14, particularly lines 50-63).

It would have been obvious to incorporate a block of 2'-O-methyl modifications at the 5' end of the sense and antisense strands, ore particularly two of such modifications at the end of each strand, as well as to incorporate cholesterol and to couple the cholesterol to the 3' end of the sense or antisense strand.

It would have been obvious to one of ordinary skill in the art at the time the invention, and a matter of routine experimentation, to use the general conditions taught by Giese et al. for making 2'-modified siRNA and to discover the optimal number and placement of 2'-sugar modifications in any siRNA molecule, such that the resulting siRNA molecule retained to ability to silence gene expression. Additionally, it would have been obvious to one of ordinary skill in the art to incorporate known modifications, such as 2'-O-methyl, to impart increased stability and functionality in any siRNA and to modify the 5' end of the sense and antisense strand to reduce off target effects as well as not introduce internal 2'-O-methyl groups into the siRNA, given that Giese et al. teaches that 2'-O-methyl modifications are beneficial but decrease silencing activity if incorporated at too many positions; and Elbashir et al. teaches that terminal modifications are well tolerated.

One would have been motivated to incorporate a cholesterol conjugate into the siRNA molecules of Giese et al. and would have been motivated to couple the conjugate molecule to the 3' end of the sense or antisense strand because Vargeese et al. teaches that cholesterol conjugates are used to facilitate delivery of molecules into a biological system such as a cell and can impart therapeutic activity by transferring therapeutic compounds such as siRNAs across cellular membranes. Since Vargeese et al. teach the advantage of conjugating nucleic acids including siRNAs to conjugates such as cholesterol to enhance the delivery of the molecule; one would have been motivated to incorporate the conjugate into the siRNA of Giese et al. to enhance the delivery thereof. Furthermore, since Giese et al. teaches chemical modifications to

enhance the stability of the siRNA molecule, one would have certainly been motivated to incorporate other means of enhancing the delivery of the molecule as well, such as cholesterol conjugation, as taught by Vargeese et al.

With regards to the cholesterol conjugate being coupled at the 3' end of the sense or antisense strand, this is considered an element of routine optimization to determine the optimal location within the duplexes of Giese et al. Moreover, Giese et al. teaches that necessity of a 5' phosphate on the antisense strand for active siRNA molecules, therefore one would have been motivated to incorporate the conjugate at the 3' end. Additionally, Vargeese et al. teaches configurations for coupling the conjugates which is within the realm of routine optimization.

It would have been prima facie obvious to perform routine optimization to determine optimal location for coupling the cholesterol conjugate of Vargeese et al., as well as to incorporate the chemical modifications of Giese and Elbashir in various combinations/locations, especially within the guidelines of Giese with regards to inactivating the sense strand and maintaining an active antisense strand, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the particular administration ranges used were other than routine, that the products resulting from the optimization have any unexpected properties, or that the

results should be considered unexpected in any way as compared to the closest prior art.

Further, Ebashir et al. teach that full 2'-O-methyl modification of both strands of the duplex as well as either sense or antisense strand alone, abolished RNAi activity. This combined with the teachings of Giese et al. that 2'-O-methyl modifications are beneficial if incorporated in a manner that does not significantly damage RNAi activity would motivate the skilled artisan to test these modifications in particular locations, particularly in terminal nucleotides, given that Elbashir et al. teaches that terminal modifications are well tolerated. It is considered a matter of routine experimentation to determine the optimum number and placement of the 2'-modifications to see how well the modifications were tolerated with respect to the functionality of the dsRNA, particularly given all that was known in the prior art regarding the benefits of incorporating 2'-O modifications to RNA.

Moreover, given that Giese et al. teach modification of siRNA to inactivate the sense strand, one would have been motivated to introduce 2'-O-alkyl groups, particularly 2-O-methyl groups at the 5' end of the sense strand to reduce off target effects and increase the specificity of the siRNA. The problem of non-target effects with antisense strands have been known in the prior art and solutions have been proposed to counteract these non-target effects. Jackson et al. discovered similar problems with antisense strands in RNAi and that when using double stranded RNA the antisense strand was also capable of non-target effects. It therefore not only would have obvious to routinely optimize the molecules for stability/activity balance, but also would have

been obvious to one of ordinary skill in the art to incorporate 2'-O modifications in the antisense strand and because Giese et al. teach modification of the sense strand at the 5' end reduced off -target effects, one of ordinary skill in the art would have looked to Giese et al. for guidance in incorporating modifications in particular nucleotides of the 5' end of the antisense strand to reduce off-target effects as well.

It is within the realm of routine optimization to combine the siRNA modifications of the prior art into various modification schematics to optimize the activity and stability of the molecule. It appears that the inventive feature upon which applicant is relying is modification of the 5' end of the sense strand to inactivate the sense strand combined with modifications of the antisense strand that yield an active strand. Importantly, this feature is taught by Giese et al. Although Giese et al. does not teach the instant specific configuration, Giese teaches that it is particularly advantageous to inactivate the sense strand of any of the RNAi forms of any of the embodiments, preferably via end modification, and more preferably a 5' end modification. Giese et al. teach that the advantage of this strategy arises from the inactivation of the sense strand which might otherwise interfere with an unrelated single-stranded RNA in the cell; that the 5' end of the antisense strand preferably has a free OH and that the 5' end of the sense strand is modified to inactivate the strand. Furthermore, Giese et al. teach that a 5'-phosphate on the antisense strand is required for siRNA function, suggesting that cells check the authenticity of siRNAs through a free 5' OH which can be phosphorylated and allow only such bona fide siRNAs to direct target RNA destruction.

Therefore, Giese teaches to inactivate the sense strand via modifying the terminal 5'nucleotide; teaches that the antisense strand requires a 5'-phosphate for function; and teaches incorporation of the instant type of chemical modification. Although Giese does not teach to specifically modify the first two nucleotides of each strand only, it is certainly within the realm of routine optimization to do so, especially given that Giese teaches throughout the document that modifications are preferably incorporated in blocks of one or more nucleotides.

Finally, one of skill in the art would have had a reasonable expectation of success at incorporating a cholesterol conjugate into the siRNA molecules of Giese et al. and would have a reasonable expectation of success when coupling the conjugate molecule to the 3' end of the sense or antisense strand because Giese et al. teaches that a 5' phosphate on the antisense strand is necessary for activity and Vargeese et al. teaches the advantages of conjugating nucleic acids such as siRNAs to conjugates such as cholesterol. One would reasonably expect for a cholesterol conjugate to benefit the delivery of the siRNA molecules of Giese et al. given the teachings of Vargeese et al.

Furthermore, one of skill in the art would have had a reasonable expectation of success in optimizing the siRNA molecules of Giese via terminally the first two nucleotides of 5'end of each strand with 2'-O-methyl modifications, given that this type of modification was known to enhance the stability and activity of siRNA molecules and that the modification needs to be minimized to retain activity, as taught by Giese and Elbashir. One would reasonably expect that incorporation of each of the prior art design

elements (modifications) in combination within the guidance of Giese et al. regarding modification for inactivating the sense strand and maintaining an active antisense strand to result in an active siRNA molecule.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Response to arguments considered pertinent to the instant rejection

Applicant argues that the instant modification schematic is not a matter of routine optimization because the claimed molecules significantly reduce off target effects in comparison to other siRNAs. However, this is not an element of the instant claims. The instant claims are compound claims and do not require any reduction of off target effects. The motivation in the art does not need to be identical to that of applicant. Additionally, and as set forth above, there was motivation in the art to reduce off target effects and to enhance the stability of the siRNA molecule, while maintaining activity. There is ample motivation in the art to terminally modify siRNA molecules with 2'-O-methyl modifications, as explained above.

Regarding result-effective variables, incorporation of the instant type of chemical modification was known to achieve a recognized result, that of enhancing stability. Furthermore, there was direction in the art to decrease off-target effects as well. Contrary to applicant's assertions, a problem of stability and off-target effects had been identified in the art and incorporation of chemical modifications, and specifically 2'-O-

methyl modifications, was known to be a solution. However, the specific incorporation of two 2'-O-methyl modifications at the 5'-end of each strand is not taught in the art. However, this is the element that would result from routine optimization of the teachings of the art regarding optimal placement and number of such modifications.

It is believed that applicant's arguments regarding off-target effects are addressed in the new rejection under 35 USC 103(a) above. Additionally, and importantly, this is not an element of the instant claims and the motivation to incorporate the instant modifications is not required to be the reduction of off-target effects.

The examiner has not set forth that Giese teaches the instant pattern specifically. That is why this is a rejection under 35 USC 103(a) rather than 35 USC 102. The instant pattern is a combination of known design elements and the art strongly suggests avoiding extreme modification with 2'-O-methyl modifications and to incorporate them on a smaller scale to maintain RNAi activity, thus pointing towards the instant schematic falling within the genus of routine optimization. Although Giese et al. teaches incorporation of these modifications in alternating blocks, the instant modifications are still incorporated in a block, just a single block rather than alternating; and Elbashir et al. suggests that terminal modifications are better tolerated than internal modifications.

Applicant argues Giese et al. teach away from 5' antisense penultimate modifications. While Giese et al. exemplifies a specific example of a 2'-O-modification of the penultimate 5' nucleotide with abolished activity, Giese et al. also teach many other modification patterns wherein the penultimate position of the 5' end of the antisense strand comprises a 2'-O modified nucleotides. Thus, Giese et al. discloses

various patterns of modifications and does not specifically teach that modification of the penultimate position of the antisense strand should always be unmodified when configuring a dsRNA for use in RNAi. The conclusion that the 5' end of the antisense strand should be kept without modifications of Giese et al. is with regards to a specific example. This example is not identical to the instant modification schematic. Furthermore, Giese et al. exemplifies other siRNA molecules that are 5'end modified on the antisense strand and did maintain activity. Therefore, the skilled artisan would be motivated to optimize siRNA molecules via testing for optimal placement of 2'-O-methyl modifications, which would not necessarily exclude the 5'antisense end.

For example, Giese et al. teach an assay wherein a preference was observed for molecules which were modified at every second nucleotide beginning with the most 5' terminal nucleotide of the antisense strand. Giese et al. teach that molecules which contained the modifications beginning with the second nucleotide at the 5' end of the antisense strand were more stable but had a strongly reduced activity in silencing. Giese et al. conclude that therefore 2'-O-methyl modifications at particularly selected positions in the siRNA duplex can increase nuclease resistance without necessarily abolishing RNAi completely (see paragraph [0191]). Furthermore, Giese et al. teach another experiment wherein the only siRNA that was efficient at mediating RNAi was modified with 2'-O-methyl modifications at the terminal 5' and 3' nucleotides of the antisense strand (see paragraph [0193]). Therefore, Giese et al. certainly would not be read by the skilled artisan as teaching an absolute avoidance of antisense 5'-end modification.

Giese et al. teaches the concept of inactivating the sense strand via terminally modifying it and teaches various embodiments throughout the document regarding the preference of incorporating modifications in blocks of one or more modification. It is considered obvious and certainly within the realm of routine optimization to extend the terminal modification by one nucleotide, given that the objective and result of inactivating the sense strand is the same.

A valid reason to terminally modify the sense strand is clearly set forth in Giese, wherein Giese teaches the benefits of terminally modifying the sense strand to inactivate it. Modifying one vs. two nucleotides is within the realm of routine optimization, given that the result is the same, sense strand inactivation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 201, 213, 220, 221, 224-226, 237, and 238 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 7,595,387. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of the patent are drawn to patently indistinguishable subject matter.

Claims 1-10 of patent '387 are drawn broadly to a double stranded polyribonucleic or polynucleotide comprising a sense strand and an antisense strand wherein the sense strand comprises a first 5' and a second 5' nucleotide comprise a 2'-alkyl modification, wherein the antisense strand comprises a first 5' nucleotide that is phosphorylated and a second 5' nucleotide comprising a 2'-O-alkyl modification, wherein the sense and antisense are capable of forming a duplex of 18-24 nucleotides, wherein all the nucleotides of each strand other than the first or second sense 5' nucleotide or the second 5' antisense nucleotide comprises a 2'-OH or a 2'H if a polynucleotide, wherein said double stranded polyribonucleotide or polynucleotide is capable of silencing any target gene with reduced off-target gene silencing, wherein the 2'-O-akly modification comprises 2'-O-methyl, wherein the polyribonucleotide comprise a 3' overhang of 1 to 6 bases on at least one of said antisense or sense strand, wherein only the first 5' antisense nucleotide is phosphorylated, wherein said polyribonucleotide or polynucleotide has reduced off-target gene silencing activity compared to a unmodified polyribonucleotide or polynucleotide.

The instant claims are drawn to a synthetic siRNA for interacting with a target mRNA of a target gene wherein the siRNA comprises a sense and antisense strand, each comprising a first and second 5' nucleotide having a 2'-O-alkyl modification, more specifically a 2'-O-methyl modification, wherein the 5' end of the antisense strand is phosphorylated, wherein the sense strand is not phosphorylated at the 5' end, wherein the siRNA comprises a 3' overhang of 1-5 nucleotides in at least one of the sense or antisense strands. The siRNA is 18-30 base pairs and is disclosed as capable of silencing gene expression with reduced off-target effects of a target gene compared to a siRNA not comprising said modifications (see paragraph 0047), which is the same as claimed by patent '387.

Thus, the claims are directed to overlapping subject matter that is obvious in view of each other.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AMY BOWMAN whose telephone number is (571)272-0755. The examiner can normally be reached on Monday-Thursday 6:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on (571) 272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMY BOWMAN
Primary Examiner
Art Unit 1635

/AMY BOWMAN/
Primary Examiner, Art Unit 1635